Electrostatic and pK_a calculations

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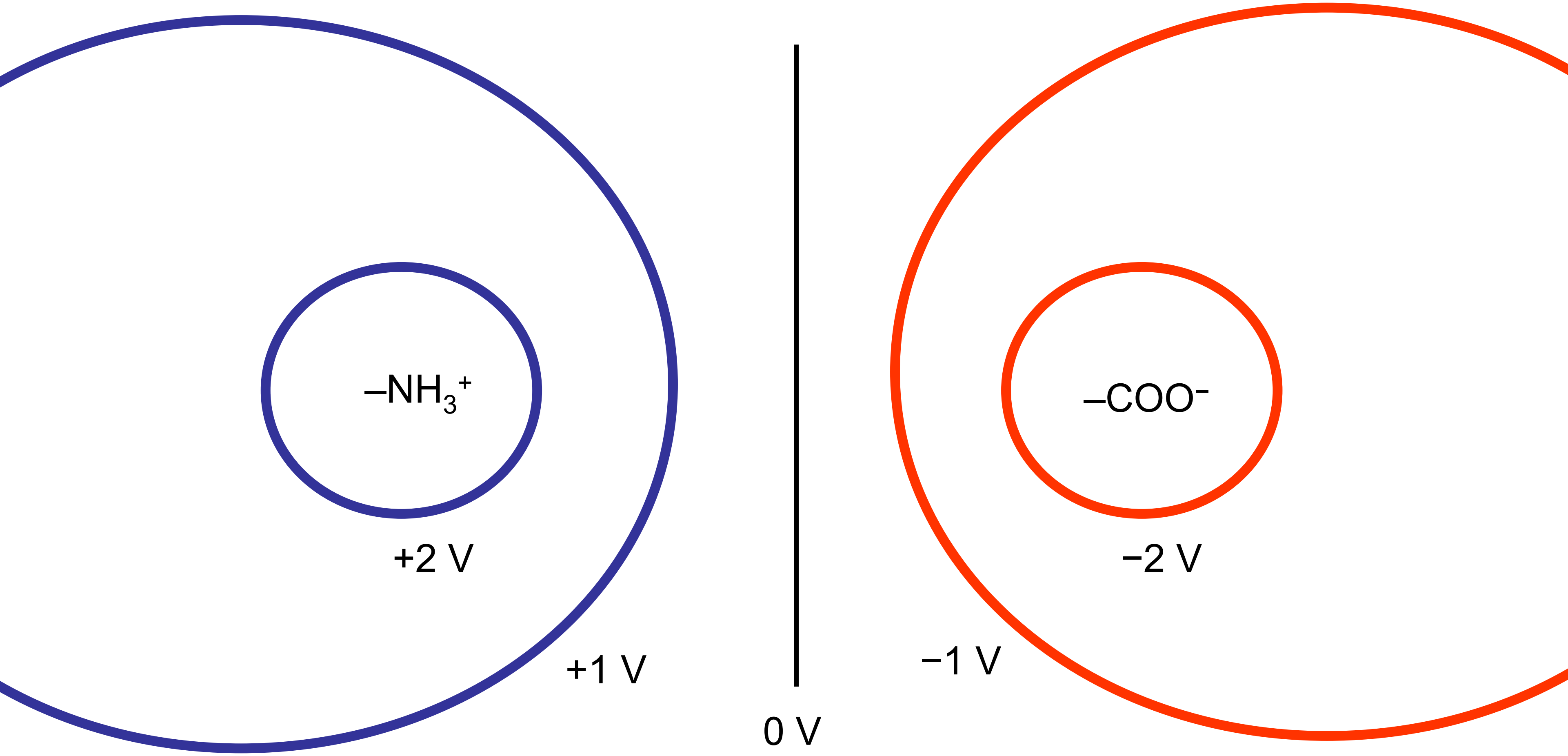
Reminder

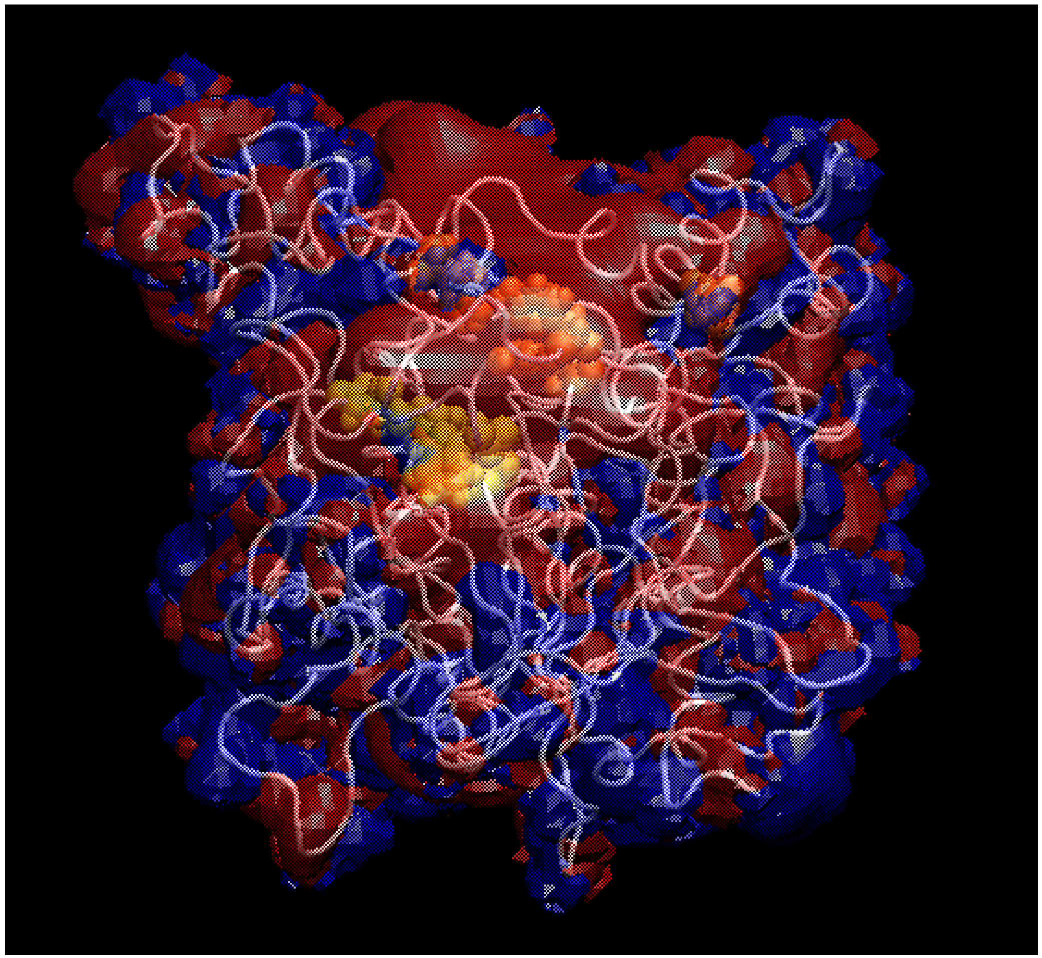
- Energy
  - $1\ \mathrm{J} = 1\ \mathrm{m}^2 \cdot \mathrm{kg} \cdot \mathrm{s}^{-2}$, the joule (What is $1kT$?)
- Potential
  - $1\ \mathrm{V} = 1\ \mathrm{m}^2 \cdot \mathrm{kg} \cdot \mathrm{s}^{-3} \cdot \mathrm{A}^{-1}$, the volt ($1\ e\mathrm{V}$? $1kT/e$?)
  - (note that $1\ \mathrm{s} \cdot \mathrm{A} = 1\ \mathrm{C}$, the coulomb)
- Force
  - A vector
  - $1\ \mathrm{N} = \mathrm{m} \cdot \mathrm{kg} \cdot \mathrm{s}^{-2}$, the newton

Potential contours



What would happen to a positive test charge?
Is it favourable to move here from infinity?

Potential contours



Coulomb's law

Charge (C)

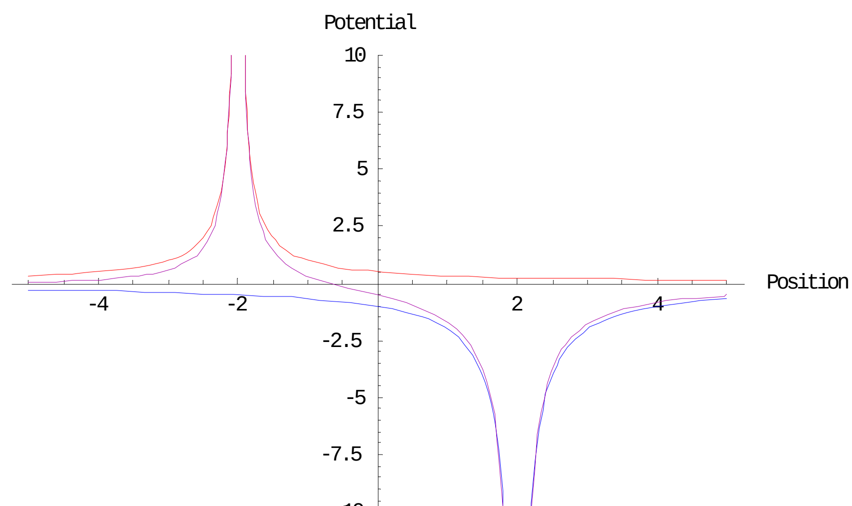
$$\phi(\mathbf{x}) = \frac{1}{4\pi\varepsilon\varepsilon_0}\sum_i \frac{q_i}{\left\|\mathbf{x}-\mathbf{x}_i\right\|}$$

Solvent dielectric ('unitless', that is, with dimensions of 1)

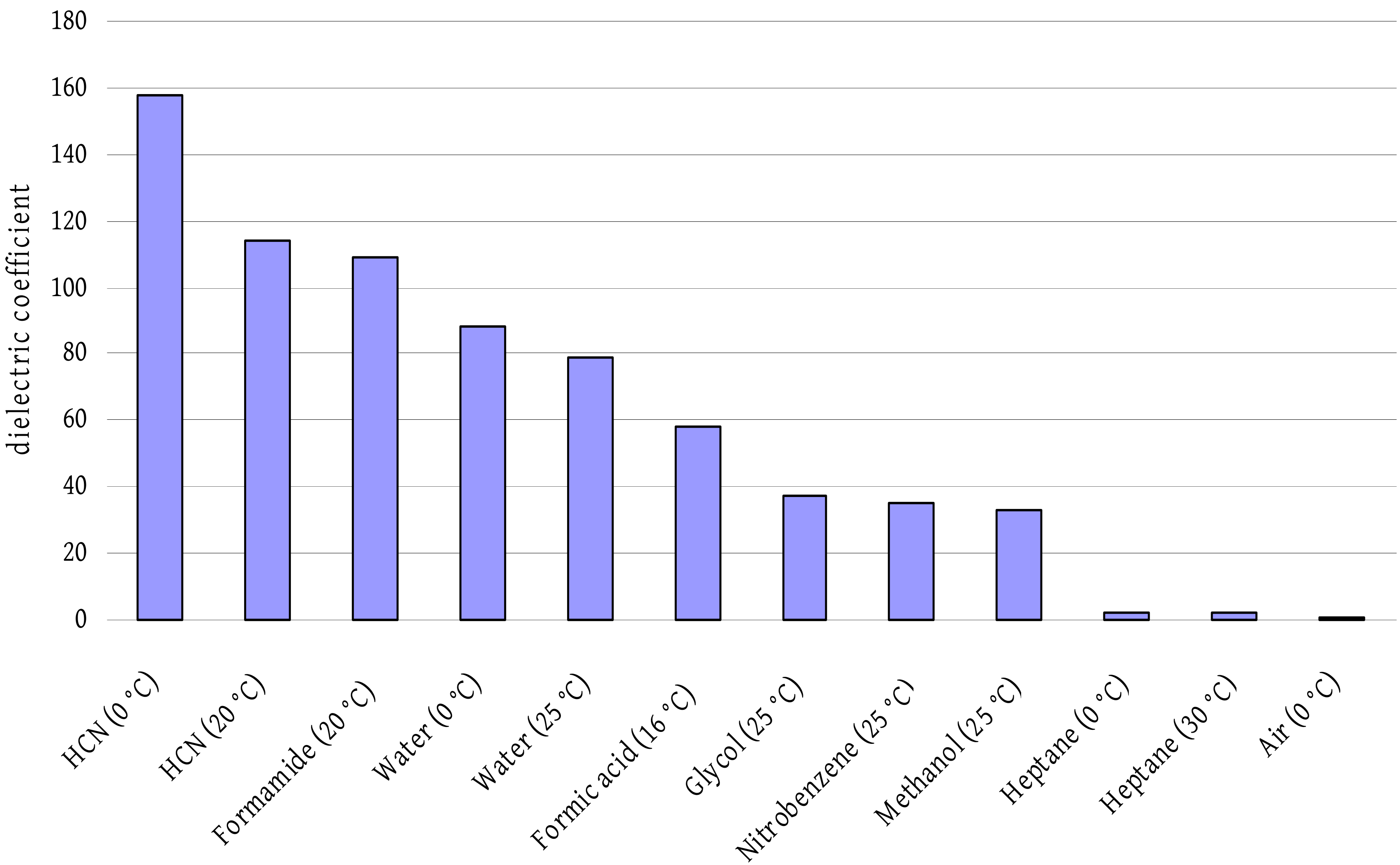
Vacuum permittivity ($8.854 \times 10^{-12}\ C^2\ J^{-1}\ m^{-1}$)

Distance (m)

- Phenomenological model (circa 1785) for charge-charge interactions in a vacuum
- Relates potential to charge for *homogeneous* dielectric materials



Dielectric coefficients



Poisson equation

- Generalize Coulomb's law to inhomogeneous dielectric coefficient

$$-\varepsilon\nabla^2\phi(\mathbf{x}) = 4\pi f(\mathbf{x}) \longrightarrow -\nabla\cdot\varepsilon(\mathbf{x})\nabla\phi(\mathbf{x}) = 4\pi f(\mathbf{x})$$

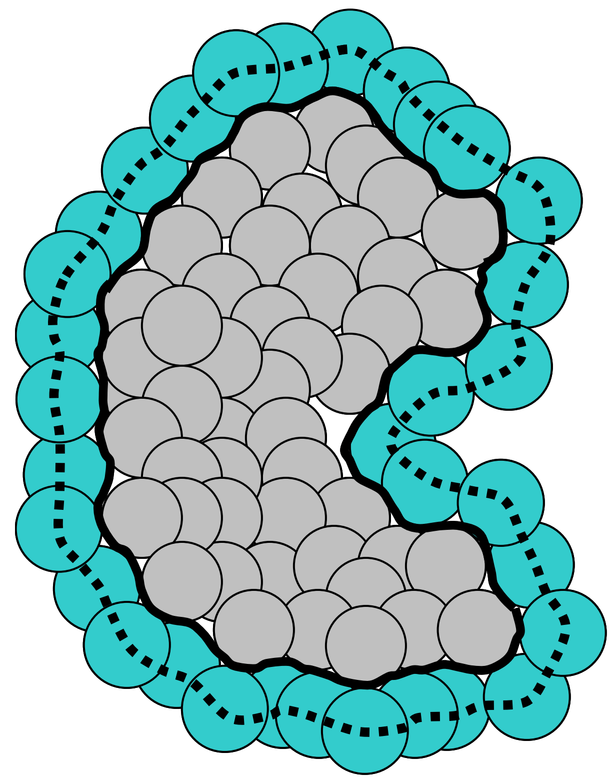
- Describes electrostatic potential due to:
  - Inhomogeneous dielectric
  - Charge distribution
- No mobile ions

$$-\nabla\cdot\varepsilon(x)\nabla\phi(x) = f(x)$$
$$= \sum_i q_i\delta(x - x_i)$$

$$\phi(\infty) = 0$$

Molecular dielectric functions

- Multiple dielectric values:
  - 1: vacuum
  - 2 to 4: atomic polarizability (solid)
  - 4 to 10: some liberation, minor sidechain rearrangement
  - 10 to 20: significant internal rearrangement
- Multiple surface definitions
  - Van der Waals
  - Splines
  - Molecular surface



Poisson equation: energies

- Total energies obtained from
  - Integral of polarization energy
  - Sum of charge-potential interactions

$$G[\phi] = -\frac{1}{4\pi}\int\left[f\phi - \frac{\varepsilon}{2}(\nabla\phi)^2\right]dx$$

$$= -\frac{1}{8\pi}\int\varepsilon(\nabla\phi)^2 dx$$

$$= -\frac{1}{8\pi}\int\phi\sum_i q_i\delta(x-x_i)dx = -\frac{1}{8\pi}\sum_i q_i\phi(x_i)$$

Poisson equation: energies

- Total energies obtained from
  - Integral of polarization energy
  - Sum of charge-potential interactions
- Numerically-calculated energies contain self-interaction terms:
  - Infinite (for analytic solution)
  - Very unstable (for numerical solution)
- Self-interactions must be removed

For Coulomb's law

$$G[\phi] = \frac{1}{2}\sum_i q_i \phi(x_i)$$

$$= \frac{1}{2}\sum_i \sum_j \frac{q_i q_j}{\varepsilon \left\| x_i - x_j \right\|}$$

$$= \frac{1}{2}\sum_i \sum_{j \neq i} \frac{q_i q_j}{\varepsilon \left\| x_i - x_j \right\|}$$

$$+ \frac{1}{2}\sum_i \lim_{x \to x_i} \frac{q_i^2}{\varepsilon \left\| x - x_i \right\|}$$

Solvation energy

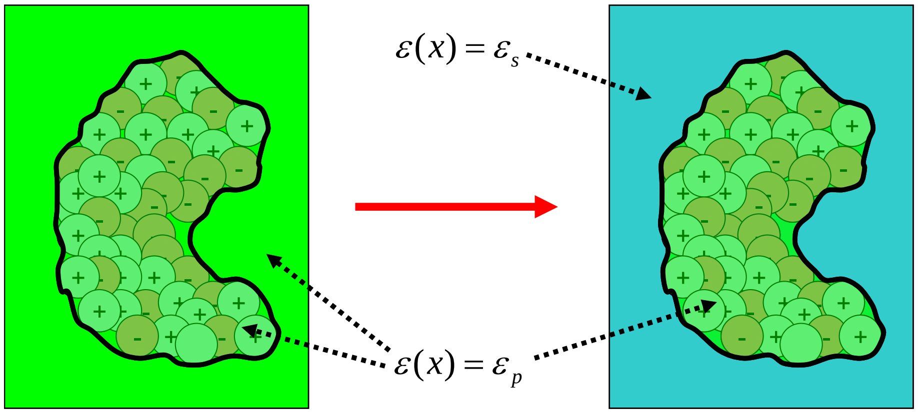
- Solvation energies obtained directly from reaction field
- Difference of
  - Homogeneous
  - Inhomogeneous

  dielectric calculations
- Self-energies removed in this process

$$\Delta_{solv} G = G\left[\phi_2\right] - G\left[\phi_2\right]$$

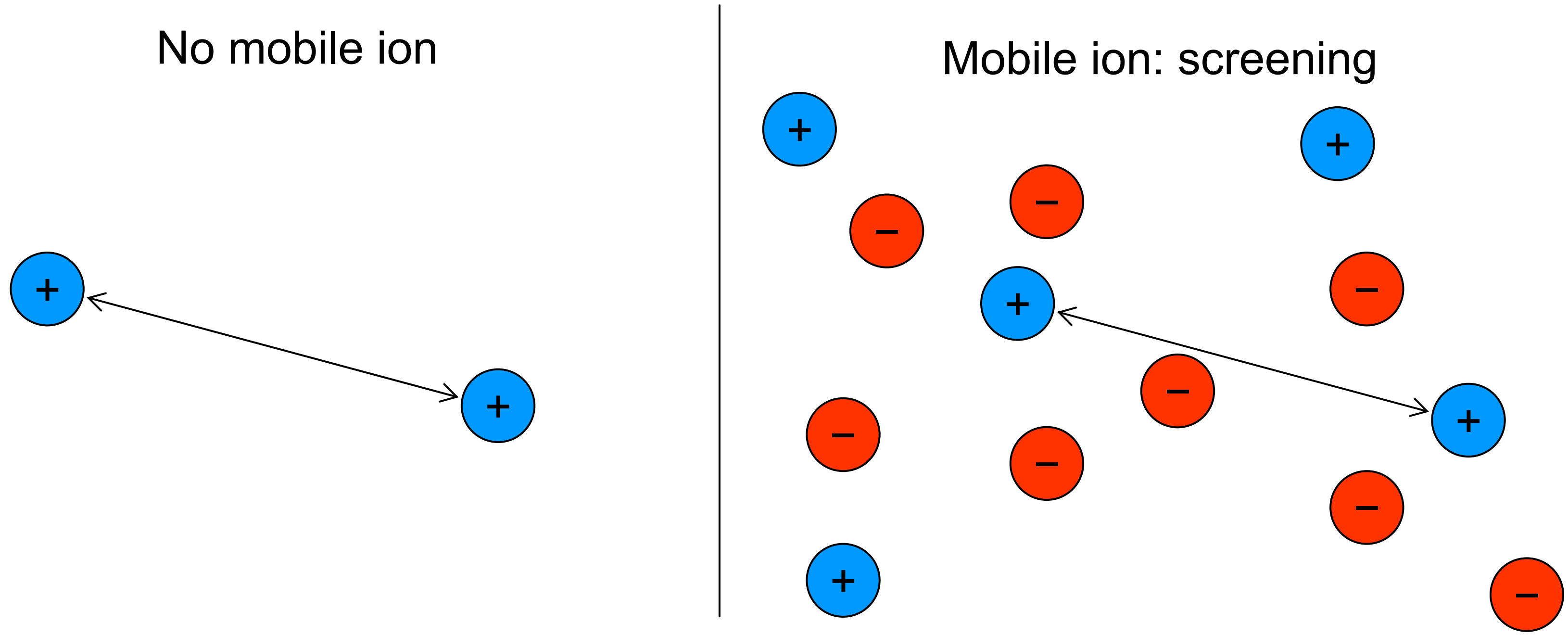
$$= \frac{1}{2}\sum_i q_i \left(\phi_2\left(x_i\right) - \phi_2\left(x_i\right)\right)$$

$$= \frac{1}{2}\sum_i q_i \varphi\left(x_i\right)$$



Screening of electrostatic potential

- Think about mobile ions
- Salt concentration in solution makes the charge on the protein ‘less effective’



Poisson-Boltzmann equation

- Screening: Debye-Hückel theory
- How do the mobile ions organize themselves?
  - Try the Boltzmann distribution
- Result: Nonlinear partial differential equation

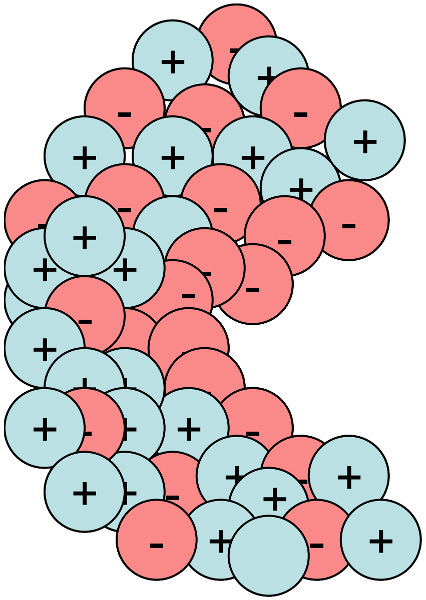
$$-\nabla \cdot \varepsilon(x) \nabla \phi(x) - 4\pi \sum_m Q_m \bar{n}_m e^{-\beta Q_m \phi(x) + V_m(x)} = 4\pi \sum_i q_i \delta(x - x_i)$$

$$\phi(\infty) = 0$$

Coefficients: charge distribution

$$-\nabla\cdot\varepsilon(x)\nabla\phi(x)-4\pi\sum_m Q_m\bar{n}_m e^{-\beta Q_m\phi(x)+V_m(x)}=4\pi\sum_i q_i\delta(x-x_i)$$

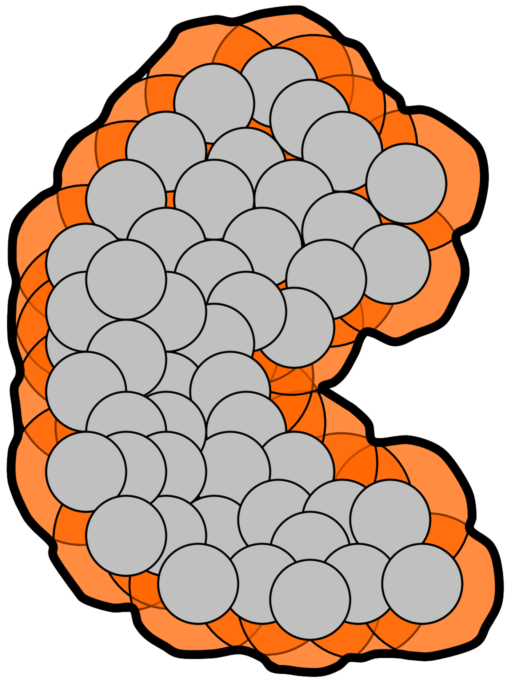
- Charges are delta functions: hard to model
- Often discretized as splines to ‘smooth’ the problem



Coefficients: mobile ion distribution

$$-\nabla \cdot \varepsilon(x) \nabla \phi(x) - 4\pi \sum_m Q_m \bar{n}_m e^{-\beta Q_m \phi(x) + V_m(x)} = 4\pi \sum_i q_i \delta(x - x_i)$$

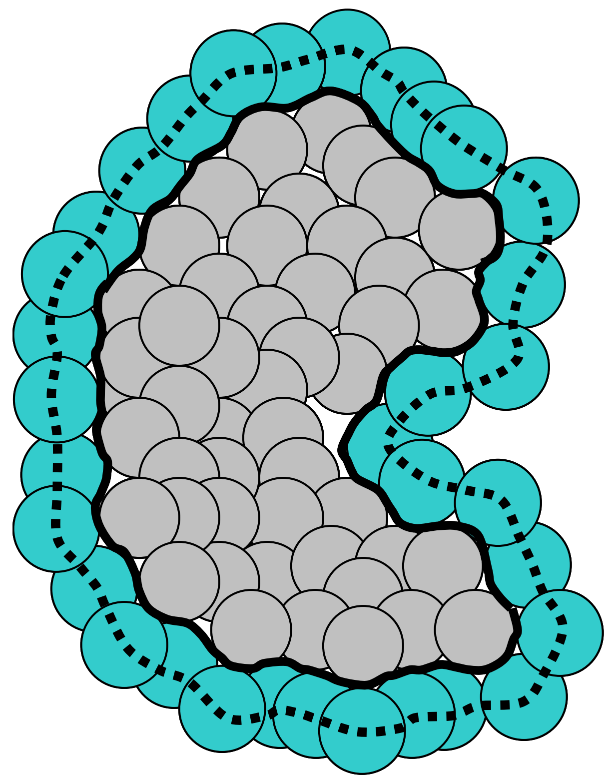
- Provides:
  - Bulk ionic strength
  - Ion accessibility
- Usually constructed based on 'inflated van der Waals radii'



Coefficients: dielectric function

$$-\nabla \cdot \varepsilon(x) \nabla \phi(x) - 4\pi \sum_m Q_m \bar{n}_m e^{-\beta Q_m \phi(x) + V_m(x)} = 4\pi \sum_i q_i \delta(x - x_i)$$

- Describes change in dielectric response:
  - Low dielectric interior (2 to 20)
  - High dielectric solvent (80)
- Many definitions:
  - Molecular (solid line)
  - Solvent-accessible (dotted line)
  - van der Waals (gray circles)
  - Inflated van der Waals (previous slide)
  - Smoothed definitions (spline-based and Gaussian)
- Results can be ***very sensitive*** to the choice of surface!!!



Poisson-Boltzmann energies

$$G[\phi] = \frac{1}{4\pi}\int\left[\rho_f\phi - \frac{\varepsilon}{2}(\nabla\phi) + \bar{\kappa}^2\left(\cosh(\phi) - 1\right)\right]dx$$

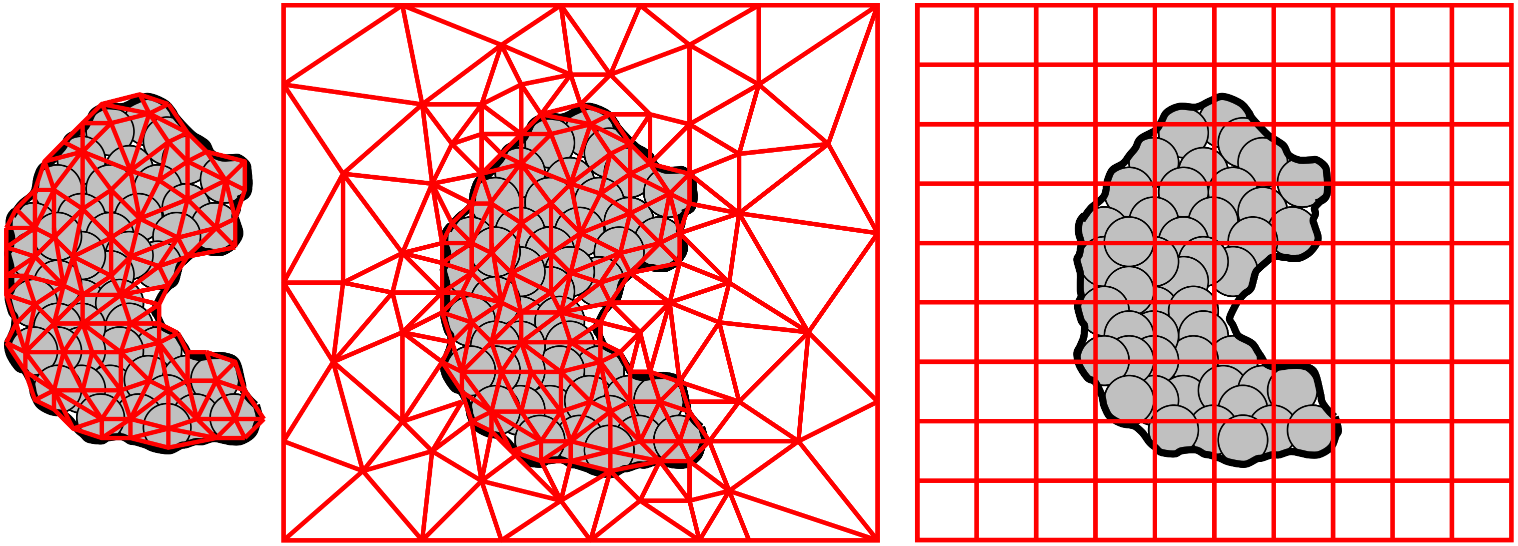
Fixed charge-potential interactions

Dielectric polarization

Mobile charge energy

Discretization: local methods

- Polynomial basis functions (defined on interval)
- 'Locally supported' on a few grid points
- Only overlap with nearest-neighbors → sparse matrices



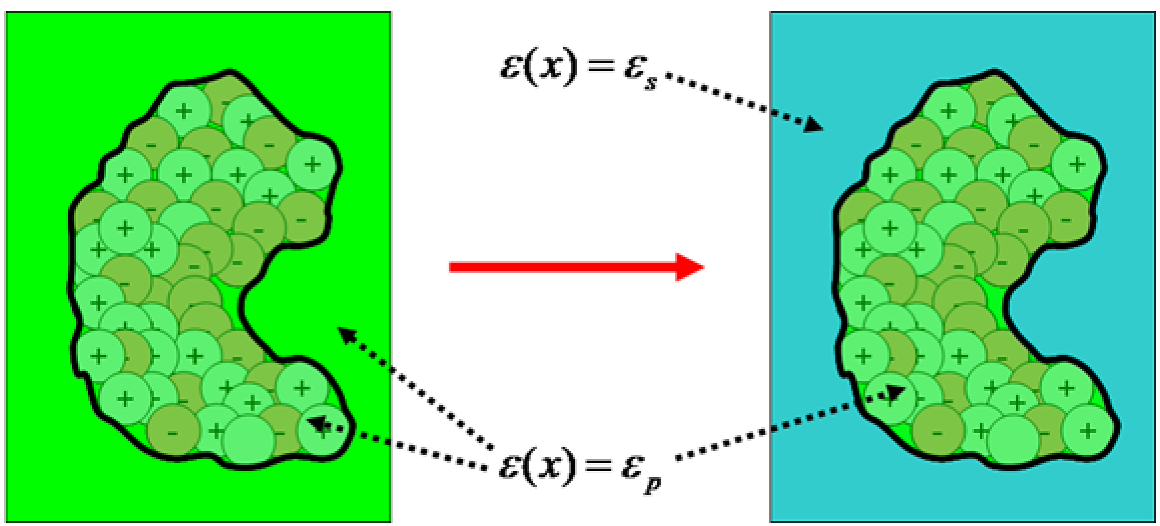
Boundary element (Surface discretization) | Finite element (Volume discretization) | Finite difference (Volume discretization)

Input and output: blackbox

- Software: APBS, WHAT IF, etc.
- Input:
  - Solute ‘pqr’: atom positions, charges, and radii
  - Solvent: dielectric constant, spatial accessibility
  - Mobile ions: ionic strength, spatial accessibility
- Output: potential contours, energies, pK_a
- Use thermodynamic cycles to obtain the desired energy values

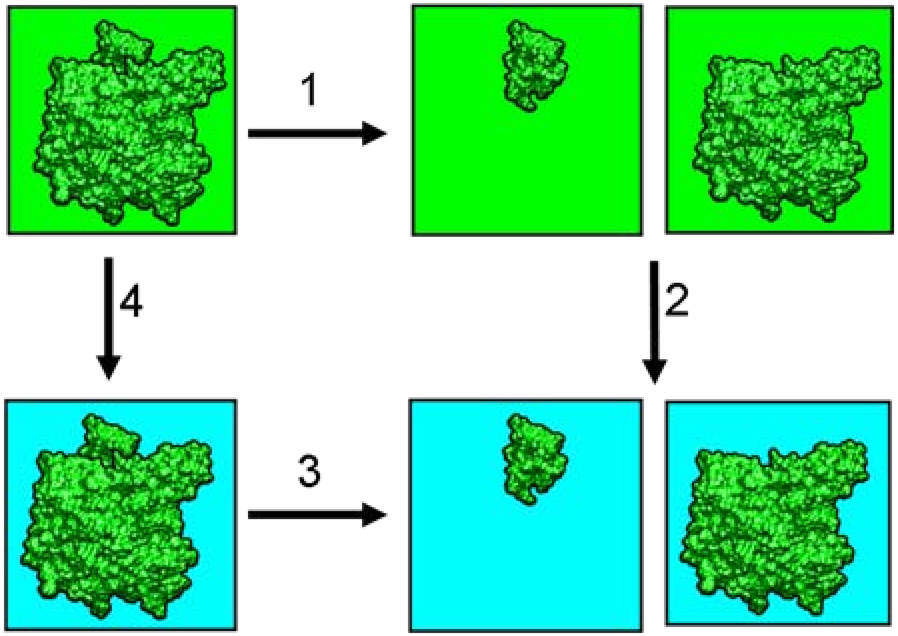
Solvation energy

- Physical model: transfer solute from dielectric of 1 (vacuum) to 80 (water)
- Computational model: transfer solute from homogeneous dielectric to inhomogeneous dielectric – eliminate self-interaction terms
- Two models can be reconciled through free energy cycle: set the 'reference state'



Binding energy

- This calculation assumes no conformational change!
- Separate calculation into two steps:
  - Calculate electrostatic interaction in homogeneous dielectric (Coulomb's law)
  - Calculate solvation energy change upon binding (Poisson or Poisson-Boltzmann equation)
- Self-interactions are removed in solvation energy calculation



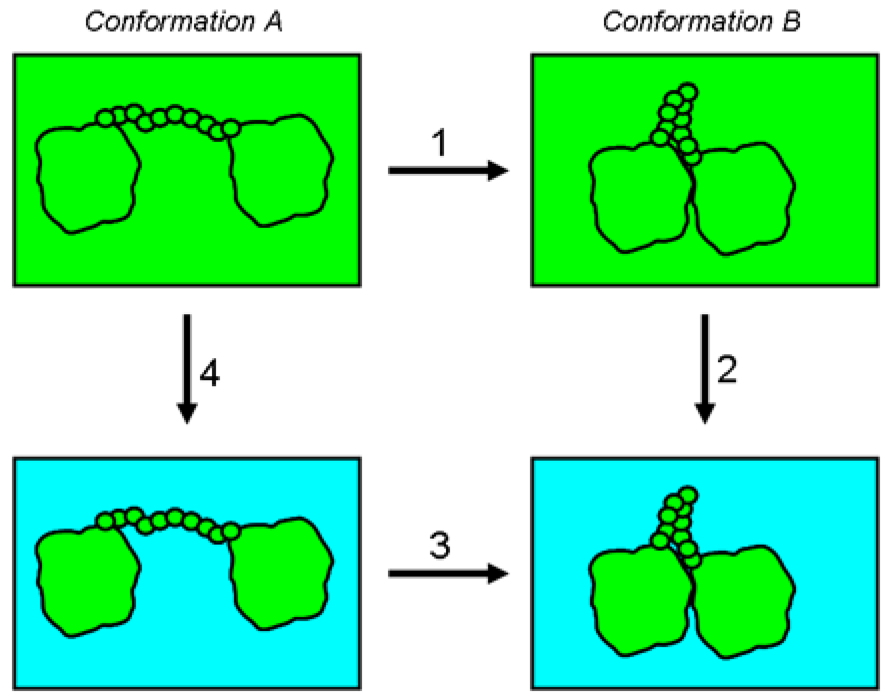
$$0 = \Delta G_1 + \Delta G_2 - \Delta G_3 - \Delta G_4$$

$$\Delta G_3 = \left(\Delta G_2 - \Delta G_4\right) + \Delta G_1$$

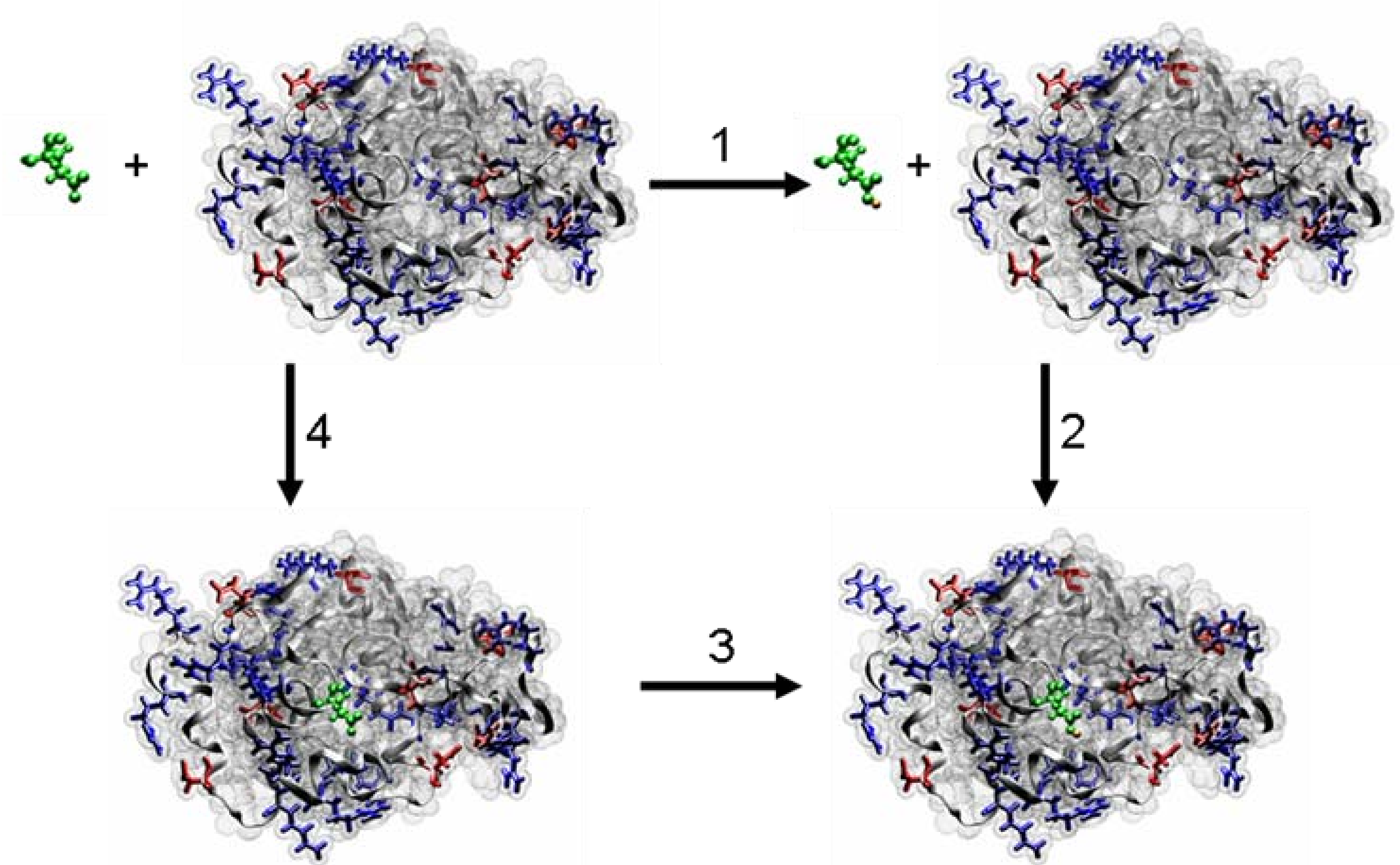
$$= \Delta\Delta G_{solv} + \Delta G_{coul}$$

Conformational changes

- Same concepts as binding energy calculation:
  - Calculate electrostatic energy due to configuration change in homogeneous dielectric (Coulomb's law)
  - Calculate electrostatic energy due to change in solvation between configurations (Poisson or Poisson-Boltzmann)



pK_a calculations



- $HA + H_2O \rightarrow H_3O^+ + A^-$ $\qquad \Delta G_a = -kT \ln K_a$
- $pK_a = -\log_{10} K_a$

pK_a calculations

- Want acid dissociation constant for residues in a particular structural context
- Use 'model' pK_as for amino acids
- Calculate pK_a from two 'binding' calculations:
  - Binding of unprotonated residue
  - Binding of protonated residue

Amino acid	α-Carboxylic acid	α-Amino	Side chain
Alanine	2.35	9.87	
Arginine	2.01	9.04	12.48
Asparagine	2.02	8.80	
Aspartic Acid	2.10	9.82	3.86
Cysteine	2.05	10.25	8.00
Glutamic Acid	2.10	9.47	4.07
Glutamine	2.17	9.13	
Glycine	2.35	9.78	
Histidine	1.77	9.18	6.10
Isoleucine	2.32	9.76	
Leucine	2.33	9.74	
Lysine	2.18	8.95	10.53
Methionine	2.28	9.21	
Phenylalanine	2.58	9.24	
Proline	2.00	10.60	
Serine	2.21	9.15	
Threonine	2.09	9.10	
Tryptophan	2.38	9.39	
Tyrosine	2.20	9.11	10.07
Valine	2.29	9.72	

Case studies from recent literature

- Oliver Beckstein, Kaihsu Tai, Mark S. P. Sansom (2004) Not ions alone: barriers to ion permeation in nanopores and channels. *J. Am. Chem. Soc.* 126:14694–14695 http://dx.doi.org/10.1021/ja045271e
- Shiva Amiri, Kaihsu Tai, Oliver Beckstein, Philip C. Biggin, Mark S. P. Sansom (2005) The α7 nicotinic acetylcholine receptor: molecular modelling, electrostatics, and energetics. *Mol. Membr. Biol.* 22:151–162 http://dx.doi.org/10.1080/09687860500063340
- Vishwanath Jogini, Benoît Roux (2005) Electrostatics of the Intracellular Vestibule of K^+ Channels. *J. Mol. Biol.* 354:272–288 http://dx.doi.org/10.1016/j.jmb.2005.09.031

Hands-on tutorials on the web

- Practical:
  - http://en.wikiversity.org/wiki/Poisson-Boltzmann_profile_for_an_ion_channel
- Adaptive Poisson-Boltzmann Solver (APBS)
  - http://apbs.sourceforge.net/
  - Prof. Nathan Andrew Baker
- pK_a calculations (WHAT IF)
  - http://enzyme.ucd.ie/Science/pKa/
  - Dr Jens Erik Nielsen